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14. ABSTRACT

The ROPO program allowed Dr. Majde-Cottrell over a 15-year period to contribute about 30 publications to distinguished journals and to advance our understanding of the molecular basis of viral pathogenesis. In addition to her scientific contributions, the ROPO program allowed her to maintain credibility in the scientific community, currency in the virology and immunology literature, and to continue a productive research effort upon retirement from ONR.

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FINAL TECHNICAL REPORT

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TITLE: Mechanisms of Cytokine Induction in Acute Viral Infections

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FINAL TECHNICAL REPORT

MECHANISMS OF CYTOKINE INDUCTION IN ACUTE VIRAL INFECTIONS

TECHNICAL DESCRIPTION:

The general problem investigated by this ROPO research is the molecular basis of the "flu" syndrome induced by common RNA viruses such as influenza. Specifically, we have investigated the role of viral double-stranded RNA (dsRNA), a byproduct of viral replication, in triggering the fever, somnolence and anorexia (elements of the acute phase response, or APR) characteristic of influenza viral infections, and characterizing the immune system hormones, termed cytokines, that are induced by virus to mediate these central nervous system responses.

SUMMARY OF ACCOMPLISHMENTS:

In the 15 years that Dr. Majde-Cottrell and I collaborated on this ROPO project we demonstrated the following: a) synthetic dsRNA (poly[rI•rC]) induces an APR (altered sleep, low body temperature, weight loss) indistinguishable from an acute influenza infection of the rabbit or mouse; b) viral dsRNA can be extracted from the lungs of influenza-infected mice that will induce an APR in the rabbit identical to that induced by poly[rI•rC]; c) pretreatment of rabbits with poly[rI•rC] will abolish the APR (i.e., induce a hyporesponsive state) to influenza virus in the same manner as influenza virus itself; d) live virus capable of producing dsRNA is required for a viral APR; e) synthetic viral dsRNA of a small size (108 base pairs) induces an APR in the rabbit; f) viral dsRNA leaches out of dying cells in vitro and is thus available to act on neighboring cells to induce cytokines; g) a component of the APR to influenza virus consists of excess slow wave sleep and reduced rapid eye movement sleep; the same sleep alterations are seen when animals are challenged with poly[rI•rC]; h) the type I interferon interferon-α, a cytokine made in large amounts during viral infections and induced by dsRNA and viruses, causes an acute phase response in rabbits identical to that induced by poly[rI•rC]; i) the APR induced by poly[rI•rC] introduced into the mouse lung has similar sleep and temperature elements as influenza virus.

All of the above findings are supportive of our hypothesis that viral dsRNA is an initiator of the viral APR and acts through cytokine induction. However, recent findings with a mouse strain genetically deficient in the receptor for type I interferons reveals that the APR induced by poly[rI•rC] is slightly enhanced in the absence of a response to type I interferons. This unexpected finding suggests that cytokines other than interferon-α are key regulators of the viral APR, and that type I interferons actually suppress viral symptoms. Furthermore, we observed that normal rapid eye movement (REM) sleep was substantially suppressed in the type I interferon receptor-deficient mouse, implying a role for endogenous type I interferons in normal sleep regulation. Interferons have previously been assumed to function only when a virus invades the body, and a physiological role for interferons in sleep regulation has never been suspected. This unanticipated finding is currently under investigation.

In addition to the above investigations on dsRNA, Dr. Majde-Cottrell has participated in several other projects in my laboratory: 1) the role of influenza viremia in triggering the neural responses to virus; 2) the role of growth hormone releasing hormone in regulating the sleep and temperature responses to influenza virus; 3) the role of inducible and neural nitric oxide synthases in the sleep and temperature responses to influenza virus; 4) the sleep response to the combined cytokines tumor necrosis factor-α and interferon-γ; and others. The influenza infection model she has brought to our laboratory is an important tool for investigating the molecular basis and functions of sleep—the basic mission of my laboratory.

Dr. Majde-Cottrell retired from ONR in September, 2002, but continues to collaborate on this project. The project is now supported by a grant from the National Institute for Child Health and Development.

SIGNIFICANCE OF THIS ROPO PROJECT TO THE NAVY:

Infectious diseases, many of viral origin, continue to account for extensive lost duty time in the military, especially in recruit training camps. Acute respiratory and gastrointestinal agents impair operational performance and occasionally abort missions and training programs. One possible approach to coping with performance decrements due to viral infections is to treat the disease rather than the infection. Cytokines probably mediate this disease process. Therefore an understanding of which cytokines are operating in acute viral infections may allow effective treatment of illness through appropriate cytokine antibodies or receptor blockers. Such reagents are under development for treating bacterial sepsis, and thus this investment can potentially be leveraged for viral disease therapy.

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